Brexpiprazole augmentation on mirtazapine for treatment-resistant depression in an elderly patient.

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Abstract :

Treatment-resistant depression (TRD) poses a significant clinical challenge, particularly in elderly patients, due to age-related physiological changes, comorbidities, and reduced medication tolerability. TRD is generally defined as a major depressive disorder (MDD) that fails to respond to at least two adequate antidepressant trials. In this case, a 64-year-old male with no prior psychiatric history presented with a two-month history of depressive symptoms including insomnia, weight loss, paranoid delusions, and social withdrawal. Mirtazapine was initiated with partial improvement. Following the addition of brexpiprazole, the patient demonstrated marked clinical improvement in mood, motivation, and daily functioning.This case underscores the complexity of treating TRD in elderly patients and highlights the potential synergistic effect of combining mirtazapine with brexpiprazole, The pharmacological complementarity of these agents may enhance antidepressant efficacy while minimizing adverse effects in geriatric populations.

Introduction:

Treatment-resistant depression (TRD), generally defined as a major depressive disorder (MDD) that does not respond to at least two different antidepressant treatments for adequate dose and adequate period of time. [1]. TRD has a high prevalence and associated morbidities, which causes challenges when trying to treat this disorder. In the United States, approximately 30.9% of adults receiving pharmacologic treatment for MDD meet the criteria for TRD [2]. The prevalence of TRD increases with age, with estimates ranging from 18% to 40% among the elderly population [3].

Standard treatment options for TRD include pharmacological and non-pharmacological approaches. Several second-generation antipsychotics, such as aripiprazole, brexpiprazole, cariprazine, and quetiapine XR, are effective adjuncts in TRD[4]. Non-pharmacologic treatments such as repetitive transcranial magnetic stimulation (TMS) and electroconvulsive therapy (ECT) are also effective [4]. When combined with medications, psychotherapies provide additional benefits for the treatment of TRD [4].

Brexpiprazole is a partial agonist at dopamine D2 and serotonin 5-HT1A and antagonist to serotonin 5-HT2A and noradrenergic α1B receptors [5]. It has demonstrated efficacy as an augmentation agent to antidepressants, offering a favorable tolerability profile compared to some

other antipsychotics [6]. This paper aims to explore the augmentation of mirtazapine with brexpiprazole in elderly patients with treatment-resistant depression.

Case Presentation:

The patient is a 64-year-old male, father of 6 children, without significant past psychiatric history and no significant family history of psychiatric illness. He has a past medical history of hypertension, hyperlipidemia, and mitral regurgitation. He presented with a lack of sleep, a lack of appetite, weight loss, and paranoid delusions for the last 2 months. Specifically, he stated that "The cars passing outside are FBI agents who are watching me." The patient completely stopped going to "schul" because he felt as if others were constantly looking at him and talking about his doings. Furthermore, he felt as if he could not face people and felt feelings of introvertedness; he lacked energy and motivation to complete daily tasks. He also presented with complaints of severe headaches, blurry vision, and muscle tension, for which an MRI was done. The MRI showed age-related changes and evidence of chronic microvascular ischemic changes, but no acute intracranial pathology. The patient was diagnosed with MDD with psychotic features and prescribed fluoxetine 10 mg. The dose of fluoxetine was increased to 20 mg once daily, and quetiapine 50 mg once a day was subsequently added. Afterward, he stated that the medication is not working, and the primary care physician (PCP) referred him to a psychiatrist.

Upon psychiatric evaluation, he stated that he is experiencing feelings of helplessness and hopelessness. The patient begins his day early in the morning, yet complains of poor sleep quality. He lacks appetite and is often sedentary throughout the day. For the last two months, he felt as if he was "walking on glass". Moreover, over a six month period, he was prescribed escitalopram 20 mg once daily and bupropion 150 mg XR. Currently, the patient is on alprazolam to manage his social anxiety. On the mental status examination, he had a depressed mood, flat affect, with normal speech with poor eye contact, and was oriented to time, place, and person. The Patient Health Questionnaire (PHQ-9) score recorded for this patient based on his symptoms was an 18 out of 27, which indicates moderately severe MDD. The patient was prescribed mirtazapine 15 mg orally at bedtime. Constipation and daytime sedation were two side effects preventing us from increasing the mirtazapine dose. He only felt a slight alleviation from depressive symptoms, but reported still feeling many of his previous symptoms. brexpiprazole 0.5 mg once daily was then added to his medication regimen. Upon the addition of the brexpiprazole, he improved significantly. He stated that he felt less feelings of hopelessness and helplessness, as well as felt more motivation to complete his daily tasks.

Discussion:

Treatment-resistant depression (TRD) is defined as a major depressive disorder that has failed to respond to a minimum of two types of treatments in the management of its symptoms for an

adequate dose and period of time [1]. Underlying medical problems or the use of concurrently prescribed medications that may produce or potentiate depressive symptoms are more common among elderly psychiatric patients [3]. Commonly, elderly patients have comorbidities such as cerebrovascular disease, Parkinson's disease, and dementia. These associated comorbidities have been seen to cause higher rates of clinical depression [3]. Due to the high rates of comorbidities in the elderly, the rates of hospitalizations increased 36% in the elderly population [7]. About antidepressant doses, elderly patients are shown to tolerate ⅓-½ of the standard dosage requirements in comparison to younger populations [3]. Therefore, the treatment of TRD is both complex and challenging in the elderly population due to the long recovery process and the lack of return to the prior state of social and occupational functioning [7].

In MDD, the usual first line of medications focuses on SSRIs and SNRIs, TCAs and MAOis. This patient was on SSRIs, but they did not prove to be beneficial and his symptoms did not improve. He was then switched to a regimen of atypical antidepressants such as mirtazapine and bupropion. He was given bupropion initially, but also did not improve from this medication. He was then started on mirtazapine.

Mirtazapine is an atypical antidepressant that is approved by the FDA. The mirtazapine mechanism of action includes the antagonism of α2(alpha2), H1, 5HT2A, 5HT2C, and 5HT3 receptors[8]. Furthermore, it has appetite- stimulating and sedative properties which help aid elderly patients with symptoms such as weight loss and insomnia, respectively[9]. Although, when given alone, its efficacy may not be enough to combat symptoms of TRD[4].

Brexpiprazole, acts as a partial agonist at 5-HT1A and D2 receptors, and antagonist at 5-HT2A and α1B receptors [10]. It is also a serotonin-dopamine activity modulator. It has a more favorable side effect profile than other antipsychotics, including less sedation and metabolic disturbance, proving to be more advantageous for the elderly population[10]

The combination of mirtazapine and brexpiprazole offers a complementary pharmacological approach that may enhance antidepressant efficacy, particularly in treatment-resistant depression in elderly patients[11]. By stabilizing dopamine and serotonin levels, anxiety and depressive symptoms are reduced without the full effects of typical antipsychotics.When used in conjunction, these agents enhance serotonergic and noradrenergic activity while stabilizing dopaminergic pathways[11]. This may result in improved mood, anxiety reduction, better sleep, and increased motivation; all of which alleviate the symptoms of TRD[11].

In this case, the patient was initially prescribed fluoxetine 10 mg once daily, but their depressive symptoms still progressed. The dose of fluoxetine was then increased to 20 mg once daily, and was also added on quetiapine 50 mg once daily, yet symptoms were still not alleviated. Over a six month period, the patient was tried on escitalopram 20 mg once daily and bupropion 150 mg XR, yet still experienced no improvement. Lastly, he was tried on mirtazapine 5 mg once daily in which he felt a slight improvement in his depressive symptoms. He was then added to

brexpiprazole 0.5 mg once daily, in which he felt an extreme difference in his depressive symptoms.

Conclusion:

This case highlights the complexity of managing treatment-resistant depression (TRD) in the elderly, where comorbidities, age-related changes, and medication tolerability must be carefully considered. Despite multiple trials of SSRIs, SNRIs, and bupropion, the patient's depressive symptoms remained persistent. However, the introduction of mirtazapine provided partial relief due to its sedative and appetite-stimulating effects. With the addition of brexpiprazole, there was a marked improvement in mood, energy, and overall functioning. This case aims to show the potential benefit of a combined pharmacologic strategy involving mirtazapine and brexpiprazole in elderly patients with TRD, especially when standard therapies prove ineffective. Further studies are needed in order to establish evidence-based protocols and research for such combinations in geriatric populations.

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